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| 09/890,416 | 07/27/2001 | Yukio Yamori | SAEGU85.001A | 1599 |

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| EXAMINER |
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ZUCKER, PAUL A

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| ART UNIT | PAPER NUMBER |
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1621

DATE MAILED: 10/22/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/890,416

Applicant(s)

YAMORI ET AL.

Examiner

Paul A. Zucker

Art Unit

1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 5-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Current Status

1. This action is responsive to Applicants' amendment of 23 July 2002 in Paper No 7.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Applicant's cancellation of claim 4 is acknowledged.
4. Applicant's addition of new claims 20-29 is acknowledged.
5. Claims 1-3 and 5-29 remain outstanding.
6. The objection to the specification set forth in paragraph 2 of the previous Office Action in Paper No 5 is withdrawn in response to Applicant's amendment.
7. The rejections under 35 USC § 112, second paragraph, set forth in paragraphs 4 - 6 of the previous Office Action in Paper No 5 are withdrawn in response to Applicant's amendment.
8. The rejections under 35 USC § 103 set forth in paragraphs 7 and 8 of the previous Office Action in Paper No 5 are withdrawn in view of Applicants' remarks with regard to the competency of Tortora et al (WO 00/64282-A1 11-2000) and in favor of the new rejections set forth below.

New Objections and Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

9. The abstract of the disclosure is objected to because it consists of more than one paragraph. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 3- 5, 7, 9-11, 14, 15, 18- 20, 22, 27 and 28 rejected under 35 U.S.C. 102(b) as being anticipated by CN1127070 (07-1996, provided by Applicants). CN1127070 discloses (Lines 5 and 7-10) a composition in the form of food product (milk powder) comprising resveratrol (3, 4',5-trihydroxystilbene, corresponding to instant formula (I)). CN1127070 further discloses (Lines 5 and 7-10) is use in the treatment and prevention of coronary disease and osteoporosis. The Examiner notes that coronary disease results from, among other things, hypertension. Claims 1, 3- 5, 7, 9-11, 14, 15, 18- 20, 22, 27 and 28 are therefore anticipated by CN1127070.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-3, 5-11, and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizutani et al (Biochemical and Biophysical research Communications 1998, 253, pages 859-863) and further in view of Caspar et al (WO 00/38620-A2 07-2000) and further in view of CN1127070 (07-1996, provided by Applicants).

Instantly claimed are food and pharmaceutical compositions comprising stilbene derivatives and methods for their use in treating and preventing the loss of bone due to osteoporosis and periodontal disease.

Mizutani teaches (Page 859, left column, first two sentences after abstract) that osteoporosis associated with estrogen deficiency after menopause is the most common cause of age related bone loss. Mizutani further teaches (Page 860, FIG.2, bottom right) the effect on ALP (Alkaline Phosphatase) activity of treatment of osteoblastic (bone forming) MC3T3-E1 cells with resveratrol (3, 4',5-trihydroxystilbene, corresponding to instant formula (I)). Mizutani further teaches (Page 859, bottom right, last sentence) pharmaceutical compositions comprising 0.1% BSA, vehicle and/or varying amounts of resveratrol. Mizutani further specifically teaches (Page 862, left column, last sentence) using resveratrol for the treatment of osteoporosis. Mizutani teaches (Page 859, right column, lines 10-13) that resveratrol

(3, 4',5-trihydroxystilbene, corresponding to instant formula (I)) is derived from grape cultivars (plants of the vitaceae family)

The difference between Mizutani and the instant invention is that Mizutani's teaching is limited to treatment of bone loss due to menopause while treatment of periodontal disease (alveolar bone loss) and use of resveratrol in foods is also instantly claimed.

Caspar, however, teaches (Page 2, line 12 – page 3, line 3) the use of resveratrol for the treatment of periodontal disease. Caspar further teaches (Page 5, line 3-page 8, line 9) pharmaceutical compositions comprising resveratrol. Caspar teaches (Page 5, line 15-19) rinses, sprays, pastes and gels as dosage forms as well.

The difference between the combined teachings of Mizutani and Caspar and the instant invention is that neither Mizutani or Caspar teach the use of resveratrol in foods is also instantly claimed. Caspar is silent with respect to employing resveratrol in food compositions.

CN1127070, however, teaches (Abstract, lines 5 and 7-10) a composition in the form of food product (milk powder) comprising resveratrol (3, 4',5-trihydroxystilbene, corresponding to instant formula (I)). CN1127070 further teaches (Abstract, lines 7-10) is use in the treatment and prevention of coronary disease and osteoporosis.

Thus the instantly claimed compositions would have been obvious to one of ordinary skill in the art. The motivation would have been to incorporate the bone loss treatment disclosed by Mizutani along with the teachings of CN1127070 to turn

compositions for the treatment of menopausal and alveolar bone loss into food products that would present a more attractive form of administration of the compositions and would lead to better patient compliance. The expectation for success would have been high since all limitations of the invention are taught by the references and all are directed to use of resveratrol.

Examiner's Response to Applicants' Remarks with regard to this Rejection

12. Applicants present several arguments with regard to this rejection. The Examiner responds to these below:

- a. Applicants argue that Mizutani merely discloses invitro experiments with osteoblastic cells and further asserts that Mizutani does not suggest use for treatment of bone loss in living organisms. The Examiner strongly disagrees and again points to Mizutani: "Mizutani teaches (Page 859, left column, first two sentences after abstract) that osteoporosis associated with estrogen deficiency after menopause is the most common cause of age related bone loss." This constitutes a clear suggestion for application of resveratrol in treatment of humans.
- b. Applicants further argue that Mizutani does not suggest pharmaceutical compositions. Again the Examiner disagrees and points to Mizutani :
"Mizutani further teaches (Page 859, bottom right, last sentence)
pharmaceutical compositions comprising 0.1% BSA, vehicle and/or varying amounts of resveratrol."

- c. Applicants further argue that ALP activity has no relationship to osteoporosis. The Examiner points out that this is irrelevant in light of the fact that Mizutani suggests (see above) the use of resveratrol for treatment of osteoporosis regardless of mechanism. This suggestion would provide motivation to the ordinary artisan.
- d. Applicants further argue, with regard to Caspar, that Caspar discloses only invitro results. While true, this does not negate caspar's teaching of the use of resveratrol for the treatment of periodontal disease. The mechanism of action, as previously discussed above, is irrelevant.
- e. Applicants further argue that caspar does not teach use of resveratrol for treating or preventing bone loss due to menopause. The Examiner agrees but points out that Caspar is relied upon for such teaching.
- f. Applicants conclude that there is no suggestion for the use of compositions of claim 1 for treating or preventing menopausal bone loss. The Examiner disagrees and directs Applicants' attention to the rejection for the motivation.

Applicant's arguments filed 23 July 2002 have been fully considered but they are not persuasive for the reasons discussed above.

13. Claims 12-19 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toppo et al (US 6,048,903 04-2000) and further in view of Mizutani et al (Biochemical and Biophysical research Communications 1998, 253, pages 859-863) and further in view of CN1127070 (07-1996, provided by Applicants).

Instantly claimed are food and pharmaceutical compositions comprising stilbene derivatives obtained from plant sources and methods for their use in treating and preventing the coronary disease and hypertension.

Toppo teaches (Column 1, lines 25-31) the link between hypercholestermia and hypertension and the effect that resveratrol, from grape skins, has on HDL/LDL levels. Toppo further teaches (Column 1, lines 49-56) pharmaceutical compositions and forms of oral and transdermal administration as well.

The difference between the invention taught by Toppo and that instantly claimed is that Toppo does not teach the hypotensive effect of resveratrol or suggest employing resveratrol in food compositions.

Mizutani , however, teaches (Page 859, right column, lines 10-13) that resveratrol (3, 4',5-trihydroxystilbene, corresponding to instant formula (I)) is derived from grape cultivars (plants of the vitaceae family). Mizutani further teaches (Page 859, right column, lines 13-19) that resveratrol inhibits oxidation of low density lipoprotein, preventing atherosclerotic changes as well as exhibiting a vasorelaxing activity in the isolated aorta of a rat, and is presumably, therefore, useful for the treatment of hypertension.

The difference between the combined teachings of Toppo and Mizutani and the instant invention is that neither Toppo or Mizutani teach the use of resveratrol in foods as is also instantly claimed.

CN1127070, however, teaches (Abstract, lines 5 and 7-10) a composition in the form of food product (milk powder) comprising resveratrol (3, 4',5-trihydroxystilbene, corresponding to instant formula (I)). CN1127070 further teaches (Abstract, lines 7-10) is use in the treatment and prevention of coronary disease and osteoporosis.

The difference between the instant invention and the teaching of miszutani Mizutani is silent with regard to pharmaceutical compositions containing resveratrol for treatment of athersclerosis and hypertension.

Thus the instantly claimed compositions and methods would have been obvious to one of ordinary skill in the art. The motivation would have been to incorporate resveratrol for the treatment of vascular diseases as disclosed and taught by Mizutani and Toppo along with the teachings of CN1127070 to turn compositions for the treatment of athersclerosis and hypertension into food products that would present a more attractive form of administration of the compositions and would lead to better patient compliance. The expectation for success would have been high since all limitations of the invention are taught by the references and all are directed to use of resveratrol.

Examiner's Response to Applicants' Remarks with regard to this Rejection

14. Applicants present several arguments with regard to this rejection. The Examiner responds to these below:

- a. Applicants argue that prevention of oxidation of LDL does not always lead to a hypotensive effect. The Examiner believes this point is irrelevant in light of the suggestion by Mizutani of such a connection. This suggestion would be deemed sufficient to motivate the ordinary artisan and is, in fact, reinforced by the teaching of Toppo.
- b. Applicants further argue that control of HDL/LDL levels does not necessarily prevent coronary disease. The Examiner agrees and points out there are many causes of coronary disease which resveratrol would not be expected to influence. This fact, however, does not mean the teachings of Mizutani and Toppo would not motivate the ordinary artisan to create the instant invention.
- c. Applicants again conclude that there is no suggestion for the instant use of the resveratrol compositions. The Examiner again disagrees and directs Applicants' attention to the rejection for the motivation.

Applicant's arguments filed 23 July 2002 have been fully considered but they are not persuasive for the reasons discussed above.

Conclusion

15. Claims 1-3 and 5-29 are outstanding. Claims 1-3 and 5-29 are rejected.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker
Patent Examiner
Technology Center 1600

October 19, 2002


Johann Richter, Ph.D., Esq.
Supervisory Patent Examiner
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